REMARKS

A check for the fee for filing an RCE accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of Time is needed, this paper is to be considered such Petition.

Claims 15, 18-24, 26-32 and 57-59 are pending in this application. Claim 1 is amended to include the limitations of cancelled claim 24 and for clarity to render it clear that hypergastrinemia is a condition precedent to development of other disorders. Claims 30 and 31 are amended to clarify antecedent basis. Claim 58 is amended to incorporate limitations of unamended claim 1 and of cancelled claim 59. Therefore, no new matter is added.

THE REJECTION OF CLAIMS 15, 21-24, 27-29 AND 57 UNDER 35 U.S.C. §102(b)

Claims 15, 21-24, 27-29, 57 are rejected under 35 U.S.C. 102(b) as anticipated by Watson *et al.* (Cancer Research, 1996), which discloses treating cancer with immunogenic composition comprising a G17 peptide. The Examiner reasons, that since, gastrin levels are elevated in cancer, the method of Watson *et al.* is the same method as the instantly claimed. The Examiner states that Watson *et al.* discloses that administration of immunogenic composition results in reduction in gastrin level, and that the level of gastrin is elevated in patients with gastric cancer.

This rejection respectfully is traversed. The rejection is moot with respect to claims 24 and 57, which are cancelled without prejudice or disclaimer.

Claims

Independent claim 15 is directed to a method for treating a mammalian subject for serum-associated hypergastrinemia, by:

(a) identifying a subject with serum-associated hypergastrinemia, but no consequent disease; and

(b) administering to subject an immunogenic composition containing a G17 peptide of SEQ ID NO: 1 or fragment thereof to the subject to thereby lower gastrin hormone levels to treat the hypergastrinemia, wherein administration of the composition is commenced prior to development of a consequent disease.

Dependent claims specify particulars of the method.

Hence, rejected claims 1 and dependent claims are directed to methods of treatment of subjects with hypergastremia, but who have not yet developed any of the diseases to which

hypergastremia contributes by administering an immunogenic composition containing a G17 peptide of SEQ ID NO: 1 or fragment thereof.

Disclosure of Watson *et al.*

Watson *et al.* discloses the immunogen, Gastrimmune and the effect of Gastrimmune on gastrin-sensitive colorectal tumors. It does not disclose anything regarding hypergastrinemia nor treatment thereof, nor does it does it disclose treatment of hypergastrinema prior to development of any consequent diseases. Watson *et al.* does not mention the word hypergastrinemia.

Analysis

The instant claims are directed to methods of treatment of hypergastremia, which is a condition distinct from cancer. Furthermore, the patients who are treated have hypergastremia, but are treated prior to development of any consequent disease. Hence, the claims do not and cannot encompass methods of treating cancer, since the treated subject has hypergastrinemia, but has not developed any consequent disease. Since Watson *et al.* discloses methods of treatment of cancer, Watson *et al.* does not disclose all elements as claims. Therefore Watson *et al.* does not anticipate any of claims 15, 21-24, 27-29 and 57.

THE REJECTION OF CLAIMS 31, 32, 18-20 and 57-59 UNDER 35 U.S.C. §103(a)

Relevant Law

In order to set forth a prima facie case of obviousness the combination of the cited references must actually teach or suggest what is claimed. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

Under 35 U.S.C. §103, in order to set forth a case of prima facie obviousness, the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. See, *e.g.*, Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); see, also, In re Papesh, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963). In addition, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

Claims 18-20

Claims 18-20 are rejected under 35 U. S. C. 103(a) as obvious over by Watson *et al.* (Cancer Research, 1996) for the reasons set forth in the rejection for anticipation of claim 15 above. The Action states that any differences between the claimed method and the teachings of Watson *et al.* "would be appear minor in nature." This rejection respectfully is traversed.

The claims

Claim 18 recites is directed to a method or treating hypergastrinemia by:
(a) identifying a subject with serum-associated hypergastrinemia, but no consequent disease; and (b) administering to subject an immunogenic composition containing a G17 peptide of SEQ ID NO: 1 or fragment thereof to the subject to thereby lower gastrin hormone levels to treat the hypergastrinemia, wherein administration of the composition is commenced prior to development of a consequent disease, and that the serum gastrin levels of the subject are reduced or maintained at a normal level. Claim 19 states that serum gastrin levels of said subject are reduced or maintained at less than 240 pg/mL, and claim 20 recites that serum gastrin levels of said subject are reduced or maintained at less than 40 pg/mL.

Teachings of Watson *et al.* and differences from the claimed methods

Watson *et al.*, teaches the immunogen, Gastrimmune and its use for treating gastrin-sensitive colorectal tumors. It does not teach or suggest anything regarding treating hypergastrinemia prior to development of any tumors. Furthermore, Watson *et al.* does not teach or suggest any level of gastrin to be achieved to mitigate the effects of hypergastremia.

Hence, claims 18-20 are not anticipated by Watson *et al.* nor obvious over Watson *et al.*, which provides no teachings relevant to the claimed methods.

Furthermore, notwithstanding the fact that the teachings of Watson *et al.* are not relevant to the claimed methods, the Examiner is reminded that that is improper to take notice of facts outside the record. Judicial notice cannot be taken unless the facts are capable of "instant and unquestionable demonstration." The Examiner is reminded that MPEP 2144.03 states:

> The Examiner may take official notice of facts outside of the record which are capable of instant and unquestionable demonstration as being "well-known" in the art. In re Ahlert, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). . . ..

In this instance, it is not "unquestionably demonstrable" that one of ordinary skill in the art has knowledge that a particular level of gastrin should be achieved to effect treatment of hypergastrinemia, particularly to treat hypergastrinemia to prevent development of consequent diseases . The Examiner therefore is required to provide documentary evidence to support the contention that determination of the level of gastrin to achieve to effect treatment for hypergastremia would be known.

Therefore, not only has the Examiner failed to set forth a *prima facie* case of obviousness, the Examiner has failed to provide references that support the incorrect premise upon which the rejection is based.

Claims 57-59, 26, 31 and 32

Claims 57, 58, 59, 26, 31, 32 are rejected under 35 U. S. C. §103(a) as unpatentable over the Background section) in view of Watson *et al.* (Cancer Research, 1996, or Int. J. Cancer, 1995) or Gevas *et al.* (U.S. Patent No. 5,607,676). The Examiner states that claim 58 and claims dependent thereon are directed to a method of treatment hypergastrinemia where another agent, such as a proton pump inhibitor, also is administered. The Examiner, without any supporting documentation states:

> It is well known that administering proton pump inhibitors to subjects having excess gastric acid results in hypergastrinemia, i.e., elevated level of gastrin peptides (such as G17 peptide), and that, in turn, hypergastrinemia leads to such complications as increased production of gastric acid, and gastric tumors. See Background Section, p. 1-2, or see Gevas et al, col. 1-2.

The Examiner states that it is obvious that such side effects of proton pump blockers are undesirable and need to be treated or prevented, and that Watson *et al.* teaches "reduction in gastrin levels in mice suffering from stomach cancer (and having elevated level of gastrin peptides) caused by administration of Gastrimmune, reduces gastrin level in vivo." The

Examiner also states that Gevas *et al.* (U.S. Patent No. 5,607,6761) teaches an immunogen composed of G17 fragments) linked to an immunogenic carrier, such as diphtheria toxoid to generate anti-gastrin antibodies, which reduce the level of gastrin and "inhibit hypergastrinemia related disorders." The Examiner concludes that it would have been:

> prima facie obvious to one of ordinary skill in the art at the time the invention was made to be motivated to use the anti-gastrin immunogen of Watson *et al.* or Gevas *et al.* to reduce level of gastrin and thus to inhibit hypergastrinemia related disorders, because it would limit the side effects caused by administration of proton pump blockers.

This rejection respectfully is traversed. It respectfully is submitted that this rejection is moot with respect to claims 57 and 59, which are cancelled without prejudice or disclaimer.

The rejected claims

Claim 58 is directed to a method for treating a mammalian subject to inhibit agent-induced gastrointestinal side-effects, by administering to the subject, who has been treated with or is being treated with an agent selected from among a histamine receptor blocker and a proton pump inhibitor, an immunogenic composition containing a G17 peptide of SEQ ID NO: 1 or fragment thereof to thereby lower gastrin hormone levels, whereby agent-induced side-effects are inhibited. Claim 31 recites that the agent is a proton pump inhibitor is selected from among omeprazole, lansoprazole, and patoprazole. Claim 32 recites that the immunogenic composition is administered after the agent. Thus, the rejected claims 58 and dependent claims are directed to methods for inhibiting gastrointestinal side-effects that occur upon administration of proton pump inhibitors and/or histamine receptor blockers.

Differences between the cited references and the claims

Alleged admissions in the background section

The section labeled "background" clearly includes subject matter that is the subject of the application, not the prior art. For example the first sentence recites:

> The invention relates to the prevention and/or treatment of hypergastrinemia by immunological control of gastrin levels.

The background art is discussed with reference to papers. None of the cited papers teaches or suggests treating hypergastrinemia as a condition, nor treating the gastrointestinal side-effects of proton pump inhibitors or histamine receptor blockers. Notwithstanding this, the background section provides no evidence that the prior art teaches suggests that hypergastrinemia is a condition for treatment nor does it suggest the use of a immunogenic composition containing a G17 peptide to reduce gastrointestinal side-effects that result from

treatment with a histamine receptor blocker and/or a proton pump inhibitor. The background section states that:

(1) "Around 90% of patients with pernicious anemia (PA) are hypergastrinemic and total gastrin levels can be up to forty times higher than normal levels." This is not a teaching that hypergastrinemia is a condition that should be treated

(2) The background continues and discusses gastrin biology and then states:

> There is a significant positive correlation between the degree of hypergastrinemia and the number of enterochromaffin-like (ECL) cells. However, the histological type of ECL cell hyperplasia is not dependent on the degree of hypergastrinemia as there is no significant difference in the gastrin levels in patients with linear or nodular hyperplasia. Once diagnosed, despite continuing elevated gastrin levels, the ECL cell hyperplasia appears to remain stable.

Again there is no teaching for treatment of hypergastrinemia nor treating hypergastrinemia that results from treatment with a histamine receptor blocker and/or a proton pump inhibitor. In fact, it states that there is no significant difference in gastrin levels in patients with linear or nodular hyperplasia and that the course of the disease is not correlated with gastrin levels.

(3) The background continues to discuss the relationship between ECL cell carcinoids, but provides no teaching for treating hypergastrinemia nor for reducing side-effects of treatment with proton pump inhibitors or histamine receptor blockers. The background continues discussing relationships betweens hypergastrinemia and other diseases, but again, there is no teaching for treatment of hypergastrinemia as a condition. **The background section states that there is no correlation between serum gastrin levels and gastric cancer in the majority of patients**.

(4) The inferences and conclusions in the background section are not those of the prior art, but of the inventors. The Office should not put form over substance. The section labeled "Background" includes a description of the invention (fist paragraph) and inferences and conclusions from prior art. The section also discusses prior art. It is apparent that the inferences are not prior art, nor did the inventors of the subject matter believe such material to be prior art.

(5) The last paragraphs of the "background" section clearly are leading to a description of the "invention" referenced in the first paragraph and discussed in the summary immediately following.

> As stated above, gastrin acts as a mitogen, and thus would not be expected to cause a cell to mutate. This hypothesis which has been confirmed in transgenic hGAS mouse studies. However, if the mucosa has

an enhanced proliferation rate, there may be an increased chance of sporadic mutation. The only example of malignant change in animal models occurring in the presence of hypergastrinemia is carcinoid in rats following long term omeprazole administration. Although this finding is particular to rats, and no other animal model produces spontaneous carcinoids, it was felt that omeprazole may have a direct carcinogenic effect. However, the proton pump inhibitor class of drugs that produce hypergastrinemia, ECL hyperplasia and ECL carcinoids in the rat, has tested negatively for genotoxicity. Subsequent studies have shown that it is not a specific drug that leads to carcinoid formation; carcinoids can also be produced by feeding with 2000 mg/kg ranitidine, loxitidine, the hypolipidemic agent clofibrate and by 75% corpectomy, all of which produce hypergastrinemia. The mediator role of gastrin was confirmed when it was shown that antrectomy in rats prevents omeprazole induced ECL cell hyperplasia. The formation of carcinoids in rats simply in the presence of hypergastrinemia may be due to their genetic background.

There is no reported evidence of hypergastrinemia producing spontaneous tumors at other sites in the gastrointestinal tract. In humans, it is evident that an additional factor may be required for ECL cells to progress from simple hyperplasia to carcinoid. In PA, the additional factor is possibly supplied by the presence of autoantibodies.

Once the cell has been transformed, exogenous gastrin can continue to promote growth. This effect may be enhanced by gastrin/CCKB receptors which are expressed de novo on adenomas. The exact point in the adenoma-carcinoma transformation sequence at which the gastrin/CCKB receptor and autocrine gastrin are expressed is not yet known. Hypergastrinemia may increase this transforming progression through the stages of the adenoma-carcinoma sequence.

In addition, treatment with agents directed against excess production of gastric acid has been found to induce parietal cell hyperplasia and hypertrophy. Recent cases were reported to suggest a correlation between gastric acid-inhibitory treatment by either proton pump inhibitors, such as omeprazole, lansoprazole, or histamine H2 receptor inhibiting agents, such as ranitidine or cimetidine, and the occurrence of fundic gland polyps (FGP).

A therapeutic method for selectively immunologically neutralizing the biological activity of the gastrin hormone would provide an effective means to control or prevent the physiopathological changes resulting from hypergastrinemia.

As disclosed in co-assigned U.S. Pat. Nos. 5,609,870; 5, 607,676; 5,622,702; 5,468,494; and 5,023,077, immunization against the G17 and G34 gastrin forms can effect neutralization of serum gastrin. The immunogenic constructs of this invention include an aminoterminal (1-9) G17 peptide or an aminoterminal (1-6) G34 peptide conjugated via a peptide spacer to an immunogenic carrier. The preferred G17 sequence is pyro-Glu-Gly-Pro-Trp-Leu-Glu-Glu-Glu-Glu [SEQ ID NO: 1] and the preferred G34 sequence is pGlu-Leu-Gly-Pro-Gln-Gly-Arg-Pro-Pro-Pro-Pro-Cys [SEQ ID NO: 2]. The preferred spacer in both constructs is a Ser-

> peptide (Ser-Ser-Pro-Pro-Pro-Pro-Cys [SEQ ID NO: 3]). The preferred immunogenic carrier is diphtheria toxoid, tetanus toxoid, keylimpet hemocyanin, and bovine serum albumin (BSA). The gastrin immunogen is defined as a conjugate of the pGlu-Gly-Pro-Trp-Leu-Glu-Glu-Glu-Glu [SEQ ID NO: 1] peptide sequence, with an amino acid spacer linked to an immunogenic carrier. The preferred gastrin immunogen is defined as a conjugate of the (1-9) amino terminal (pGlu-Gly-Pro-Trp-Leu-Glu-Glu-Glu-Glu [SEQ ID NO: 1]) peptide which is linked by peptide spacer to diphtheria toxoid. It is further known that the gastrin immunogen preparation is also effective for inhibiting the incompletely processed or progastrin type gastrin precursors which may be bound to the cell membrane of a gastrin producing cell.
>
> There is a need in the art for compositions and methods to effectively treat hypergastrinemia. [emphasis added]

Hence, the background **prior art** provides no admission that "hypergastrinemia leads to such complications as increased production of gastric acid, and gastric tumors" as urged by the Examiner, and provides no admission that treatment of hypergastrinemia was previously known in the art. The so-called admissions are inferences made by the instant inventors in a application drafted such that the sections are not clearly delineated. Substance should prevail over form.

The background section fails to teach methods for the treatment of hypergastrinemia, an essential element of all pending claims. Further, the background section does not teach or suggest administration of an immunogenic composition comprising a G17 peptide or fragment thereof before, during or after treatment with a histamine receptor blocker and/or a proton pump inhibitor

Gevas *et al.*

Gevas *et al.* similarly provides not teaching for treatment of hypergastrinemia, and fails to cure this deficiency. Gevas *et al.* is directed to a method for treatment of "gastrin-induced disorders." Gevas *et al.* (col. 2, lines 52-59) states:

> [t]his invention provides a novel immunological approach to the control and regulation of gastrin induced disorders such as peptic ulcers. According to the invention, antibodies are induced in the patient by active immunization with immunogens that selectively target specific forms of gastrin. Alternatively, the patient can be passively immunized with anti-gastrin antibodies specific for certain forms of gastrin.

Gevas *et al.* does not teach or suggest that hypergastrinemia is a disorder nor does it teach any methods for treating hypergastrinemia. Gevas *et al.* clearly provides no teaching or suggestion for treating hypergastrinemia that results from treatment with a histamine

receptor blocker and/or a proton pump inhibitor. In fact, the **word hypergastrinemia** does not appear in Gevas *et al.*

Watson I and Watson II

Each of these references teaches the immunogen, Gastrimmune and its use for treating various tumors. Neither reference teaches methods for treatment of hypergastrinemia nor for treating hypergastrinemia that results from treatment with a histamine receptor blocker and/or a proton pump inhibitor.

Watson I describes the effect of Gastrimmune on gastrin-sensitive colorectal tumors. It does not teach or suggest anything regarding treating hypergastrinemia. Watson II describes the effect of Gastrimmune on the *in vivo* growth of rat colon tumor cells, and concluded that "tumor-induced levels" of gastrin were reduced about 40% (see, page 882, column 2). The levels of gastrin only are mentioned in the context of cancer. No mention is made that would suggest treatment of hypergastrinemia as a condition.

The combination of teachings of the cited references does not result in the claimed methods

As discussed above, the instant claims are directed to methods for inhibiting the side effects of administration of a histamine receptor blocker and/or a proton pump inhibitor by administering to the subject, who has been treated with or is being treated with a histamine receptor blocker or a proton pump inhibitor, an immunogenic composition containing a G17 peptide to inhibit the agent-induced side-effects. None of the cited art, singly or in combination teaches or suggests that hypergastrinemia should be treated nor that treating it **will reduce agent-induced side effects.**

None of the cited references mentions hypergastrinemia nor treating agent-induced side-effects; the background provides no teaching nor suggestion for treating agent-induced side-effects. None of the references nor background recognize hypergastrinemia as a health condition worthy of treatment. None suggest there is any reason to treat side-effects of administration of a histamine receptor blocker or. a proton pump inhibitor. Absent such teachings in any of the cited references and alleged admission, the combination of teachings of the cited references and alleged admission cannot and does not result in the instantly claimed methods inhibiting the side effects of administration of a histamine receptor blocker or a proton pump inhibitor.

The Examiner states:

> Applicant argues that Background Section does not provide any teaching or admission that hypergastrinemia is a condition for treatment. Examiner

> respectfully disagrees. The Background section teaches that patients with pernicious anemia (PA)are hypergastrinemic (about 40-times elevated total gastrin level; p. 1, lines 11,12), that the degree has significant positive correlation with the fundic enterochromaffin-like cells (p. 2, lines 9-11, 25-28), and hypergastrinemia may be responsible for development of gastric cancer in PA patients (p. 3, top). Thus, specification clearly suggests that hypergastrinemia is undesirable event leading to development of disorders. In addition, the Background section teaches that hypergastrinemia is a side effect of administration of proton pump inhibitors (p.3, bottom).

This is not a correct characterization of the background section. Page 3 at the bottom states:

> Long-term treatment with omeprazole is known to induce ECL cell hyperplasia which is related to the serum gastrin level.

This statement does not teach or suggest administering an immunogenic composition containing a G17 peptide or fragment thereof **to reduce side effects from** administration of proton pump inhibitors or histamine receptor blockers. There is no teaching or suggestion in the background section nor in any art of record that the side-effects can be treated with a composition containing a G17 peptide or fragment thereof nor is there a teaching or suggestion for treatment of such side-effects.

As noted above, the background section, states that there is no correlation between serum gastrin levels and gastric cancer in the majority of patients. The background section, particularly when discussing prior art, does not demonstrate that those of ordinary skill in the art at the time of filing of the application believe that **hypergastrinemia is a condition for treatment should be treated, and there is no teaching in the background section for administering immunogenic composition containing a G17 peptide or fragment thereof before, during or after treatment with a proton pump inhibitor or a histamine receptor blocker.**

To combine these references to result in the claimed methods relies on the improper use of hindsight

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

It is only the application at issue that teaches or suggests that hypergastrinemia is a condition that needing treatment; it is only the instant application that teaches (and not as background) treating side-effects of a histamine receptor blocker or a proton pump inhibitor

by administering an immunogenic composition containing a G17 polypeptide. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

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In view of the, amendments and remarks herein, reexamination and allowance of the application are respectfully requested.

Respectfully submitted,

Stephanie Seidman
Reg. No. 33,779

Attorney Docket No. 171181-059US2/2838BUS
Address all correspondence to:
Fish & Richardson P.C.
12390 El Camino Real
San Diego, California 92130
Telephone: (858) 678-5070
Facsimile: (202) 626-7796
email: seidman@fr.com